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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,277	07/25/2006	Guoqiao Li	13796-00002-US	4870

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CONNOLLY BOVE LODGE & HUTZ, LLP
P O BOX 2207
WILMINGTON, DE 19899

EXAMINER	
ARNOLD, ERNST V	

ART UNIT	PAPER NUMBER
1616	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,277	LI ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 7* is/are rejected.

7)☒ Claim(s) *5, 6 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/29/09 has been entered.

Claims 1-4 have been cancelled. Claims 5-8 are new and under examination.

Withdrawn rejections:

Applicant's amendments, Declaration, and arguments filed 10/29/09 are acknowledged and have been fully considered. Applicant cancelled all previously pending claims rendering the rejection of claims 1-4 under 35 U.S.C. 103(a) as being unpatentable over Giao et al. (Poster Abstract International Symposium on Malaria Control in the Mekong Region Dec 10-13, 2002) in view of Abstract of EP0290959 and White (Phil Trans R Soc Lond B 1999, 354, 739-749) and Lai et al. (US 2004/0058981) and Klayman (Science 1985, 228(4703), 1049-1055) moot.

Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Objections

Claim 5 is objected to because of the following informalities: Claim 5 does not end in period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 5 introduces new matter as the claim recites the limitation: "primaquine an amount up to 0.6 parts" There is no support in the specification for this limitation. The limitation of: primaquine an amount up to 0.6 parts " was not described in the specification as filed, and person skilled in the art would not recognize in the applicant's disclosure a description of the invention as presently claimed. The specification discloses: "primaquine, 0-0.2 part" on page 1 but does not describe the instantly claimed limitation. There is no guidance in the specification to

select "primaquine an amount up to 0.6 parts" and from MPEP 2163.06: "Applicant should therefore specifically point out the support for any amendments made to the disclosure." Applicant has not directed the Examiner to the support in the specification for the amendments. Therefore, it is the Examiner's position that the disclosure does not reasonably convey that the inventor had possession of the subject matter of the amendment at the time of filing of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 5 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giao et al. (Poster Abstract International Symposium on Malaria Control in the Mekong Region Dec 10-13, 2002) in view of Abstract of EP0290959 and White (Phil Trans R

Soc Lond B 1999, 354, 739-749) and Lai et al. (US 2004/0058981) and Klayman (Science 1985, 228(4703), 1049-1055).

Applicant claims:

> 5. (New) A composition useful for treatment of malaria in humans consisting essentially of artemisinin, piperaquine and primaquine formulated into tablets or granules, suppository, suspension syrup or dry powder for pediatric use in following ranges of ratios:
> artemisinin 1 part
> piperaquine 3-9 parts
> primaquine an amount up to 0.6 parts

Determination of the scope and content of the prior art

(MPEP 2141.01)

Giao et al. teach the combination of **dihdyroartemisinin, piperaquine**, trimethoprim and **primaquine** (Abstract). Giao et al. teach 64 mg dihydroartemisinin, 640 mg piperaquine, 180 mg trimethoprim and 10 mg primaquine. If the dihydroartemisinin is taken as 1 part then there are 10 parts piperaquine, about 3 parts trimethoprim and 0.15 parts primaquine.

Abstract of EP0290959 teaches combinations of **artemisinin**, dihydroartemisinin or other artemisinin derivatives with one or more of the antimalarials including **primaquine** (Abstract).

White teaches the use of combinations of antimalarials to overcome parasite resistance and to *always* use a combination with **artemisinin** or one of its derivatives (Abstract and page 746, (n)-(p)). White teaches the concept of triple combinations of antimalarials and that artemisinin and its derivatives have been combined with other

antimalarials and have accelerated recoveries, increased cure rates, reduced transmissibility and appear to have delayed the development of further resistance and reduced incidence of disease (page 746, (n)).

Lai et al. teach the equivalence of **dihydroartemisinin and artemisinin** (claim 1, 2, 4). Lai et al. teach powders and tablets (claim 9) as well as suppositories ([0037]), suspensions ([0035]), syrups and granules ([0032]) that can be formulated.

Klayman teaches that **artemisinin** has been known in traditional Chinese medicine as a treatment for fever and malaria for many centuries (Abstract). Klayman teaches that **dihydroartemisinin** is more potent than **artemisinin** (Derivatives of QHS, left column, page 1053).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

1. The difference between the instant application and Giao et al. is that Giao et al. do not expressly teach the artemisinin and the other components in the instantly claimed ratio of components. This deficiency in Giao et al. is cured by the teachings of Abstract of EP0290959, Lai et al., Klayman and White.

2. The difference between the instant application and Giao et al. is that Giao et al. do not expressly teach the composition in various formulations for pediatric use and wherein the primaquine can be formulated into a separate tablet to be taken along with a tablet of mixed artemisinin and piperaquine. This deficiency in Giao et al. is cured by the teachings of Lai et al.

Finding of prima facie obviousness

Rational and Motivation (MPEP 2142-2143)

1. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use artemisinin, as suggested by Lai et al. and White, in the composition of Gaio et al. and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because White says to *always* use artemisinin in combinations and Lai et al. establish that artemisinin and dihydroartemisinin are functional equivalents. However, from the teachings of Klayman, it is known that dihydroartemisinin is more potent than artemisinin and therefore an adjustment of the amount of ingredients would be required to maintain the same efficacy. This is then simply a matter of routine optimization to arrive at the instantly claimed 1 part artemisinin to 3-9 parts piperaquine to up to 0.6 parts primaquine. The amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. The criticality of 9 parts of piperaquine has not been shown and would be obvious to one of ordinary skill in the art given that Giao et al. teach 10 parts of the piperaquine in the absence of evidence to the contrary.

2. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was make different formulations for pediatric use, as suggested by Lai et al., in the composition of Gaio et al. and wherein the primaquine can be formulated into a separate tablet to be taken along with a tablet of mixed artemisinin and piperaquine and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Lai et al. establish the types of formulations one of ordinary skill in the art can formulate artemisinin. Pediatric use is intrinsic to the composition. Regarding the formulation of primaquine into a separate tablet and taken with a mixed tablet of artemisinin and piperaquine, it is the Examiner's position that formulation of the actives into one or more tablets is merely a design choice by one of ordinary skill in the art in the absence of evidence to the contrary. The end result remains the same; the prescribed amount of active ingredients are delivered to the patient.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

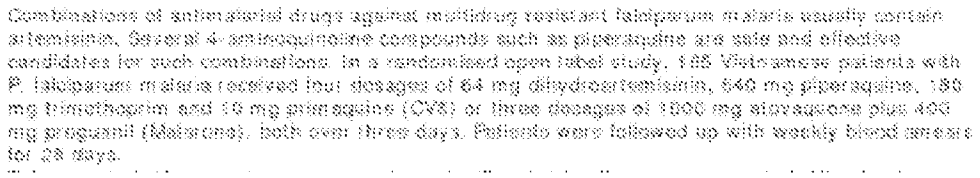
Response to arguments:

Applicant asserts that the phrase “consisting essentially of” excludes trimethoprim which is used in the composition taught by Giao et al. However, it is the Examiner’s position that from MPEP 2111.03: For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, “consisting essentially of” will be construed as equivalent to “comprising.” The composition still functions as an anti-malarial and so the basic and novel characteristics have not been changed and Applicant has not shown how the additional component would materially change the characteristics of Applicant's invention. ***The Examiner notes that a claim reciting "consisting of" would exclude all other ingredients.***

The Declaration under 37 CFR 1.132 filed 10/29/09 is insufficient to overcome the rejection of claims 5 and 7 based upon Giao et al. (Poster Abstract International Symposium on Malaria Control in the Mekong Region Dec 10-13, 2002) in view of Abstract of EP0290959 and White (Phil Trans R Soc Lond B 1999, 354, 739-749) and Lai et al. (US 2004/0058981) and Klayman (Science 1985, 228(4703), 1049-1055) because of the following analysis.

With regards to the decreased side effects, it appears that this is *an expected* result. The dosing regimen is only 4 tablets of the inventive composition containing 62.5 mg artemisinin, 312.5 mg piperaquine and 2 mg primaquine (1750 mg total) and the dosing regimen of the comparative is 8 tablets of 40 mg of dihydroartemisinin and 320 mg of piperaquine phosphate (2880 mg tota). So is it not to be expected that one would experience more side effects when taking more of a drug?

However there appears to be unexpected that Applicant can use a reduced dosage amount in a shorter time period (see paragraph 11 of the Declaration). The primary reference of Giao et al. teaches 4 doses over 3 days.



Combinations of antimalarial drugs against multidrug resistant falciparum malaria usually contain artemisinin. Several 4-aminoquinoline compounds such as piperaquine are safe and effective candidates for such combinations. In a randomized open label study, 185 Vietnamese patients with P. falciparum malaria received four dosages of 64 mg dihydroartemisinin, 640 mg piperaquine, 180 mg trimethoprim and 10 mg primaquine (CV8) or three dosages of 1000 mg atovaquone plus 400 mg proguanil (Malarone), both over three days. Patients were followed up with weekly blood smears for 28 days.

The total amount of actives is: 64 + 640 + 180 + 10 = 894 mg active per dose X 4 doses = 3576 mg total actives over 3 days which is more total active than the comparative in the Declaration paragraph 11.

The problem is that the inventive ratio of actives (62.5 mg artemisinin, 312.5 mg piperaquine and 2 mg primaquine) is 1:5:0.032 which is commensurate in scope with the limitations of instant claim 6 (see above) but not instant claim 5. Presently, there is a full order of magnitude difference between the amount of primaquine claimed and that which was shown. Therefore, the Examiner reasonably concludes that the showing of objective evidence is not commensurate in scope with the claimed subject matter.

Conclusion

Claims 2 and 8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

The Examiner encourages Applicant to request an interview before filing a response to this Office Action to address the rejections above such that an allowance may result pending a search update at that time.

Since no independent claim is allowable, then no claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ernst V. Arnold whose telephone number is 571-272-8509. The examiner can normally be reached on M-F (7:15 am-4:45 pm).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ernst V Arnold/
Primary Examiner, Art Unit 1616